UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/808,885	03/14/2001	Jennifer L. Hillman	PF-0354-2 DIV	5250

27904 7590 09/30/2002

INCYTE GENOMICS, INC.
3160 PORTER DRIVE
PALO ALTO, CA 94304

EXAMINER
HARRIS, ALANA M

ART UNIT	PAPER NUMBER
1642	7

DATE MAILED: 09/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/808,885	HILLMAN ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *1,2,7,9,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3, 5, 6, 8 and 10-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II (claims 3, 5, 6, 8, 11, 12 and 14-17) in Paper No. 6, received July 2, 2002 is acknowledged. The traversal is on the ground(s) that Group III (claims 4, 7, 9, 18 and 18) and Group IV (claims 10 and 13) are from "...the same scope as the claims of Group II that could be examined together with the claims of Group II without undue burden". This is found partially persuasive. Upon reconsideration the Examiner will rejoin Group II and Group IV. However, Group III will not be rejoined with Group II for the reasons set forth in the restriction requirement (Paper No. 4, mailed May 30, 2002). As to the question of burden of search, the claims of the two different Groups, antibodies versus a method of using the said antibodies are classified differently, necessitating different searches in the U.S. Patent shoes. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement set forth in Paper #4 except for the rejoinder of Groups II and IV is deemed to be proper and is adhered to.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-19 are pending.

Claims 1, 2, 4, 7, 9, 18 and 19, drawn to non-elected inventions are withdrawn from examination.

Claims 3, 5, 6, 8 and 10-17 are examined on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 3, 5, 6, 8 and 10-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The limitations of claim 1 are read into the examined claims. Claim 1 is broadly drawn to "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ. ID. NO: 1". Claims 3, 5, 6, 8 and 10-17 are drawn to antibodies (i.e. monoclonal, humanized and polyclonal) and methods of making the said antibodies that specifically bind the fragments listed in claim 1. The specification while being enabling for the polypeptide having the amino acid sequences of SEQ. ID. NO: 1 and the antibodies that bind SEQ ID NO: 1, does not reasonably provide enablement for variants that have at least 90% sequence identity and antibodies that bind said variants.

There is no guidance as to how to make these divergent sequences, which possess function in the absence of any information, on what functions the native protein possesses. Furthermore, there is no guidance as to how specific antibody binding would be to the 90% naturally occurring variants. Likewise, it would seem that specific function(s) would be required to make the said antibodies useful for the applications disclosed in the specification. The specification does not teach what those are or how to determine what they are. This could possibly be a vast collection of antibodies. The specification provides inadequate instruction to allow one skilled in the art to make and use the said naturally occurring polypeptides having at least 90% sequence identity and their resulting antibodies with a reasonable expectation of success and without undue experimentation.

5. Claims 3, 5, 6, 8 and 10-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitations of claim 1 are read into the examined claims. Claim 1 is broadly drawn to "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ. ID. NO: 1" and biologically-active and immunogenic fragments. Claims 3, 5, 6, 8 and 10-17 are drawn to antibodies (i.e. monoclonal, humanized and polyclonal) and methods of making the said antibodies that specifically bind the fragments listed in claim 1. Claim 3 is broadly drawn to an isolated antibody

that specifically binds to a purified polypeptide comprising an amino acid sequence selected from a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO: 1, biologically-active fragment of the amino acid sequence of SEQ ID NO: 1 and an immunogenic fragment of the amino acid sequence of SEQ ID NO: 1. These claims are drawn to antibodies that are to bind SEQ ID NO: 1 and polypeptide fragments that possibly contain a small number of amino acid residues that is less than the 290 amino acids. Hence the claims are drawn to antibodies that bind amino acid residues that minimally contain only portions of SEQ ID NO: 1. Thus, the claims are drawn to a large genus of molecules. In the case of antibodies that allegedly bind small identified amino acid residues claimed with open language, the genus of polypeptides comprising only a partial sequence encompasses a variety of subgenera with widely varying attributes. The specification discloses only the alleged structural features of one species of antibody, those that bind the polypeptide sequences of SEQ ID NO: 1. The specification lacks information to lead one of skill in the art to understand that the applicant had possession of the broadly claimed invention at the time the instant application was filed. Applicant is referred to the interim guidelines concerning compliance with the written description requirement of 35 U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1 and 3 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 3 is vague and indefinite because it depends from non-elected claim 1. For examination purposes, the limitations of non-elected claim 1 will be read into the examined claims. Applicants may obviate this rejection by rewriting the claim in independent form.

b. Claim 1 is vague and indefinite in the recitation "biologically-active fragment". It is not clear what activities are bestowed upon these designated fragments described by this term.

Claim Rejections - 35 USC § 101

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 3, 5, 6, 8 and 10-17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and a substantial asserted utility or a well established utility.

Applicants have asserted several utilities for the claimed antibodies (i.e. monoclonal, chimeric and fragments thereof), which bind specifically to the annexin binding protein set forth in SEQ ID NO: 1 and fragments thereof. The specification asserts the following utilities for the claimed antibodies: compositions for the diagnosis, prevention or treatment of cancer, immune disorders and neurological disorders. However, these asserted utilities are not credible, specific or substantial for the broadly

claimed polypeptide. Other that the sequence identification number, the specification provides no functional characterization of SEQ ID NO: 1, no specific tissue distribution of the polypeptide and no specific disease state in which these proteins affect. The broadly claimed antibodies specifically bind to polypeptides belong to a group, collectively referred to as annexin binding proteins, NABP. This protein according to the specification, page 4, last paragraph can be obtained from any species (i.e. bovine, equine or human) and from any source whether natural, synthetic or recombinant. The NABP-1 protein identified as SEQ ID NO: 1 is reportedly expressed in a wide variety of cells and tissues, see page 21, lines 26-31. Agonists and antagonists of NABP-1 polypeptides such as the claimed antibodies are suggested to prevent or treat immune disorders, cancer and neurological disorders encompassing different tissue types, see page 22, lines 8-28. Consequently, there is no information that links expression of the claimed polypeptide to **any specific** tissue or disorder. Thus, the asserted utility of the claimed antibodies is not substantial, specific or credible.

Claims 3, 5, 6, 8 and 10-17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 3, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohsawa et al. (Journal of Neurochemistry 67:89-97, 1996/ IDS Reference #2) or Accession number P70488 (February 1, 1997), in view of Campbell in view of Campbell, Ailsa M. (Laboratory Techniques in Biochemistry and Molecular Biology 13:1-32, 1984). Ohsawa and the said accession number teach both a biologically-active fragment and an immunogenic fragment of SEQ ID NO: 1, see amino acid database sheet and page 93, Figure 3(c). Ohsawa and Accession #P70488 do not teach a monoclonal antibody which specifically binds to the polypeptide comprising the amino acid sequence of SEQ ID NO:1 or to the recited fragments of the polypeptide.

However, Campbell teaches a strategy to generate antibodies, as well as methods for producing hybridomas, procedures of monoclonal antibody production in mice and monoclonal antibodies from hybridoma cell lines with high biological activity (e.g. affinity, specificity, etc.), see page 3, Figure 1.1. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize the teachings of both, the referenced patent and Campbell. In addition Campbell states on page 29, Section 1.3.4 "It is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)." One of ordinary skill in the art would have been motivated to immunize an animal, such as a rat with the polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or a fragment of the

polypeptide to aid in the establishment of hybridomas secreting antibodies able to bind with high specificity.

12. Claims 3 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohsawa et al. (Journal of Neurochemistry 67:89-97, 1996/ IDS Reference #2) or Accession number P70488 (February 1, 1997), in view of Bird et al. (Science 242:423-242, 1988). Ohsawa and the said accession number teach both a biologically-active fragment and an immunogenic fragment of SEQ ID NO: 1, see amino acid database sheet and page 93, Figure 3(c). Ohsawa and Accession #P70488 do not teach a single chain antibody which specifically binds to the polypeptide comprising the amino acid sequence of SEQ ID NO:1 or to the recited fragments of the polypeptide.

However, Bird teaches the production of a single-chain antigen-binding protein and efficacy of single-chain antibodies. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to produce single-chain antibodies. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Bird that single-chain antibodies are advantageous because of their small size, lower background in imaging applications, less immunogenic and ability to be designed with specialized function, see page 426, column 1.

13. Claims 3, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohsawa et al. (Journal of Neurochemistry 67:89-97, 1996/ IDS Reference #2) or

Accession number P70488 (February 1, 1997), in view of Huse et al. (Science 246:1275-1281, December 8, 1989). Ohsawa and the said accession number teach both a biologically-active fragment and an immunogenic fragment of SEQ ID NO: 1, see amino acid database sheet and page 93, Figure 3(c). Ohsawa and Accession #P70488 do not antibodies produced by screening a Fab expression library or a recombinant immunoglobulin library, wherein the said antibodies specifically bind to the polypeptide comprising the amino acid sequence of SEQ ID NO:1 or to the recited fragments of the polypeptide.

However, Huse teaches procedures for the generation of Fab fragments and a large combinatorial library of the immunoglobulin repertoire in phage lambda. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to produce Fab fragments, catalytic and other antibodies. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Huse that the applicability of such a screening library in the generation and construction of bacteriophage lambda libraries enables the expression of a population of functional antibody fragments with potential diversity (see page 1276, column 1, first full paragraph) and these types of antibodies are useful in diagnostics and biosensors (see page 1280, column 2, last paragraph).

14. Claims 3, 5, 6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohsawa et al. (Journal of Neurochemistry 67:89-97, 1996/ IDS Reference #2) or Accession number P70488 (February 1, 1997), in view of U.S. Patent number

6,180,370 (filed June 7, 1995). Ohsawa and the said accession number teach both a biologically-active fragment and an immunogenic fragment of SEQ ID NO: 1, see amino acid database sheet and page 93, Figure 3(c). Ohsawa and Accession #P70488 do not teach an antibody which specifically binds to the polypeptide comprising the amino acid sequence of SEQ ID NO:1 or to the recited fragments of the polypeptide, wherein the antibody is a chimeric antibody or a humanized antibody.

However, U.S. Patent #6,180,370 teaches the production of chimeric antibodies (see column 11, lines 55-67) and humanized antibodies (see column 11, line 1-column 12, lines 4). The patent also teaches several composition formulations comprising the said antibodies and acceptable excipients, as well as labels, which can be joined to the antibodies, see column 19, line 35-column 20, line 31. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to produce and design chimeric and humanized antibodies and label and produce a therapeutic admixture comprising the said antibodies. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in the patent that the applicability of such manufactured antibodies would provide antibodies specific to a predetermined antigen with strong affinity, see bridging paragraph of columns 10 and 11. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by additional teachings in the patent that antibodies taught in patent '370 could be comprised with an acceptable excipient within a composition for therapeutic and diagnostic purposes.

15. Claims 3 and 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohsawa et al. (Journal of Neurochemistry 67:89-97, 1996/ IDS Reference #2) or Accession number P70488 (February 1, 1997), in view of Harlow and Lane (Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, 1988). As previously discussed, the aforementioned reference teaches a biologically-active fragment and an immunogenic fragment of SEQ ID NO: 1, see amino acid database sheet and page 93, Figure 3(c). Ohsawa and Accession #P70488 do not teach a method of preparing a polyclonal antibody which specifically binds to the polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or to the recited fragments of the polypeptide, nor the said polypeptides in a composition such as an adjuvant contained with saline, mineral oil or aluminum hydroxide.

Harlow and Lane teach the production of polyclonal antibodies and the said antibodies in a pharmaceutically acceptable diluent, such as Freund's adjuvant. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce polyclonal antibodies in order for functional and clinical studies as well as the formulation a pharmaceutical composition comprising a carrier/excipient and the polypeptides of claim 1 in order to store the polypeptides in solution for the purpose of making an adjuvant. One of ordinary skill in the art would have been motivated to store the polypeptides in saline because Harlow and Lane teach that these components are necessary when producing an effective adjuvant. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in placing the polypeptide fragments of claim 1 in a pharmaceutically

acceptable carrier such as saline because this protocol is a standardly used immunological technique described in basic antibodies manual such as Harlow and Lane.

Because pharmaceutically acceptable carriers such as sterile saline solution and phosphate-buffered-saline solution were well known in the art, one of ordinary skill would have known how to formulate a pharmaceutical composition comprising a carrier/excipient and the instantly claimed polypeptides.

When the claim is directed to a product, the preamble or intended use is generally nonlimiting if the body of the claim is directed to an old composition and the preamble merely recites a property inherent in the old composition. [*Kropa v. Robie*, 88 USPQ 478, 480 - 81 (CCPA 1951); see also MPEP 2111.02]. Thus, art which reads on a compound may also be applied to pharmaceutical compositions consisting essentially of said compound and a suitable pharmaceutical carrier.

It has been held by the Court that a compound and a carrier are obvious, if it is obvious in the art to utilize a carrier with related compounds. See In re Rosicky, 125 USPQ 341 (CCPA 1960).

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4315 for regular communications and (703) 308-4315 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

ALANA HARRIS
PATENT EXAMINER

Alana M. Harris, Ph.D.
September 26, 2002